Best Practice

STRAIGHT TO THE POINT

Menopause and hormone-replacement therapy: Part 2. Hormone-replacement therapy regimens

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HORMONE-REPLACEMENT THERAPY REGIMENS

- It is important to review the goals of hormone-replacement therapy (HRT)—for example, treatment of menopausal symptoms vs prevention of osteoporosis—with the patient before initiating therapy (table 1)
- Efficacy of HRT should be assessed after 4 to 6 weeks; doses can be titrated upward until symptoms are relieved. The need for continued therapy can be evaluated every 4 to 6 months
- HRT may be given orally, transdermally, or intravaginally in either continuous or cyclical schedules
- Progesterone is usually given with estrogen for women with a uterus to prevent endometrial hyperplasia

Common forms of estrogen (in equivalent doses) include

- Conjugated equine estrogen (CEE; for example, Premarin),* 0.625 mg
- 17β-estradiol (for example, Estrace), 2.0 mg
- Ethinyl estradiol (for example, Estinyl), 0.02 mg
- Transdermal 17β-estradiol (for example, Climara, Estraderm), 0.05 mg

*Trade names are given for information only and do not represent endorsement of any of the products by the authors or this journal.

Table 1 *Summary of hormone-replacement treatment effects**

Condition	Estrogen alone	Estrogen plus progestin	Raloxifene HCl	Estrogen plus testosterone	Biphosphonates
Hot flashes and urogenital symptoms	++	++	−	++	oo
Mood, cognitive libido changes	+	+	oo	+	oo
Osteoporosis	++	++	++	++	++
Coronary artery disease	+/−	+/−	o	o	oo
Stroke	oo	−	o	o	oo
Breast cancer	−	−	++	o	oo
Endometrial cancer	− −	oo	oo	o	oo
Deep venous thrombosis or pulmonary embolus	− −	− −	− −	o	oo

HCl = hydrochloride.
*++ = proven benefit; + = possible benefit; − − = proven risk; − = possible risk; oo = no effect; and o = no data.

- Women without a uterus do not require progesterone
- Uterine bleeding that is excessive, prolonged, or in any way different from the expected bleeding of the prescribed regimens must be evaluated promptly with endometrial biopsy, ultrasonography, or both
- Premenstrual-like symptoms (breast tenderness, bloating, mood swings, headache) can occur when HRT is initiated. Many resolve spontaneously within a few months. Lowering the progesterone dose or switching from cyclical to continuous HRT can help

Standard-dose continuous oral HRT

- CEE, 0.625 mg orally daily, with MPA, 2.5 mg orally daily (Prempro combines these into 1 tablet) (table 2)
- Withdrawal bleeding occurs in a spotty, unpredictable manner but usually abates after 6 to 8 months because of endometrial atrophy
- Women who are many years past menopause may have less bleeding
- For the relief of hot flashes, some women require higher doses of estrogen (up to 1.25 mg of CEE, rarely 2.5 mg). These should be tapered as soon as possible to a lower maintenance dose

Continuous dosing may be easier for some women than cyclical dosing.

Standard-dose cyclical oral HRT

- CEE, 0.625 mg daily, with MPA, 5 or 10 mg, on days 1 through 10 of each month
- Withdrawal bleeding occurs monthly after day 10 of progestin and can continue for years
- Cyclical HRT is available in a combination pill (Premphase) in which progesterone is present only in the pills for days 12 through 28

Premenstrual-like symptoms (breast tenderness, fluid retention, nausea, headache) are more prominent with cyclical HRT.

Low-dose oral HRT

- CEE, 0.3 mg daily (with progesterone, if needed)
- Low-dose HRT may be sufficient to treat hot flashes in some women. Low-dose HRT appears to preserve bone mineral density (BMD),[1] but there are not yet studies evaluating fracture risk

[1] *Genant HK, Lucas SJ, Weiss S, et al. Low dose esterified estrogen therapy effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Estratab/Osteoporosis Study Group. Arch Intern Med 1997;157:2609-2615*. Randomized controlled trial that observed 406 women for 2 years. A dose of 0.3 mg daily significantly increased BMD at the spine and hip, decreased low-density-lipoprotein (LDL) levels, and increased high-density-lipoprotein (HDL) levels without causing endometrial hyperplasia.

Transdermal HRT

- Avoids first-pass hepatic metabolism and has a theoretic advantage for women who have a history of gallbladder disease, chronic liver disease, and hypertriglyceridemia
- The patch is available with estrogen alone or in a combination of estrogen and progesterone

Intravaginal HRT

- Systemic absorption varies
- Helpful for menopausal patients in whom atrophic vaginitis is the predominant symptom, but provides some relief of hot flashes
- Typical use is cyclical (3 weeks on, 1 week off)

Common forms of progesterone

- Medroxyprogesterone acetate (MPA; for example Provera)
- Micronized progesterone
- Norethindrone

Oral contraceptives

- Are often recommended for symptomatic perimenopausal women with regular or nearly regular menses (follicle-stimulating hormone [FSH] level, <20 IU/L). Norethindrone acetate, 0.5 to 1 mg, plus ethinyl estradiol, 20 to 35 µg, is a common formulation
- Provide an added benefit of pregnancy prevention, although the absolute risk of conception is low
- Most women are switched to HRT when the FSH level rises or at age 50 because the estrogen content of HRT is lower than in oral contraceptives

Table 2 *Hormone replacement and related agents*

Drug (trade name)*	Dosage forms, mg	Usual dose	Adverse effects, comments
Conjugated estrogens (Premarin)	0.3, 0.625, 1.25, 2.5	0.625 mg orally daily	Nausea; use caution in patients with liver disease
Medroxyprogesterone acetate (Provera)	2.5, 5, 10	2.5 mg orally daily	
or		5-10 mg orally daily on the first 10 days of each month	Breast tenderness, bloating, breakthrough bleeding
Conjugated estrogens plus medroxyprogesterone (Prempro)	0.625, 2.5	1 tablet orally daily	
Estrogen vaginal cream (Premarin)	0.625/g	0.5-2 g daily	3 wk on, 1 wk off
Estradiol transdermal system (Estraderm)	0.05-0.1/24 h	1 patch twice a wk	3 wk on, 1 wk off; must use oral progestins
Norethindrone acetate plus ethinyl estradiol	1.0/5 μg	1 tablet orally daily	
Calcium carbonate (Caltrate 600)	1,500 (600 mg calcium)	1 tablet orally twice a day	Constipating
Vitamin D (calcitriol) (Rocaltrol)	0.25 μg	0.25 μg orally daily	
Calcium carbonate plus vitamin D (Caltrate Plus)	1,500 (600 mg calcium); 200 IU	1 tablet orally twice a day	
Alendronate sodium (Fosamax)	10	10 mg orally daily	
or		70 mg orally weekly	Must be taken on an empty stomach; remain upright for 30 minutes to avoid reflux esophagitis
Risedronate sodium (Actonel)	5	5 mg orally daily	
or		35 mg orally weekly	Same as for alendronate
Clonidine HCl (Catapres)	0.1, 0.2, 0.3	0.1 mg orally daily to twice a day	
Clonidine HCl (transdermal) (Catapres-TTS)	0.1, 0.2, 0.3/24 h	1 patch weekly	

HCl = hydrochloride.
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- After atrophic vaginitis is relieved, some women are able to taper use to once a week for maintenance
- Concomitant progestins are not indicated for short-term use but should be considered for long-term use in women who still have their uterus